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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,700	10/15/2004	Monica Petronella Maria De Maat	101137-56	2836

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EXAMINER	
SAUCIER, SANDRA E	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,700	DE MAAT ET AL.	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007 and 04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6,9-12,14-34,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *10 and 14-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6,9,11,12,25-34,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-4, 6, 9-12, 14-34, 36, 37 are pending. Claims 2-4, 6, 9, 11-13, 25-34, 36, 37 are considered on the merits. Claims 10, 14-24 are withdrawn from consideration as being drawn to a non-elected invention.

Specification

Applicants have clarified the passage in the specification by explaining that an error was made. However, applicants may not introduce new matter into the specification. Therefore, the amendment to the specification MUST BE CANCELED.

The amendment filed 4/408 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

SCOPE of ENABLEMENT

Claim 12 remains rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method to inhibit or prevent tumor growth by administration of a fibrin matrix. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The prior art teaches that the presence of a fibrin matrix, protects tumors from destruction by cytotoxic cells (Gunji *et al.* [U]), and prevention of fibrin matrix formation enhances the cytotoxic destruction of tumor cells, (Vaage *et al.* [V],) and that fibrin coagulation prevents induction of LAK activity (Atagi *et al.* [W]). Thus, the prior art does not support the claimed method, nor is the claimed method shown in a working example in the specification. Thus, the claimed method is not enabled.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

As set forth in *In re Fisher*, 427 F2.d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. *Ex parte Humphreys*, 24 USPQ2d, 1260.

INDEFINITE

Claims 2-4, 6, 9, 11-13, 25-34, 36, 37 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because they depend on a varying composition of fibrinogen variants as the starting material. A claim may be rendered indefinite by reference to an object that is variable. For example, the Board has held that a limitation in a claim to a bicycle that recited "said from and rear wheels so spaced as to give a wheelbase that is between 58 and 75 percent of the height of the rider that the bicycle was designed for" was indefinite because the relationship of parts was not based on any known standard for sizing a bicycle to a rider, but on a rider of unspecified build. *Ex parte Brummer*, 12 USPQ2d 1653 (Bd. Pat. App. & Inter. 1989).

Also, new claims 36 and 37 state that the HMW fibrinogen is at least 80%, or is not more than 70%, but fails to state % of what. Is this molar or weight %

or some other measure. Also, is the denominator of this %, total fibrinogen or something else. Percentages are always indefinite unless the numerator and denominator and the units are defined.

Response to Arguments

Applicant argues that the present claims are method claims and argues about infringement issues. First, this is not an infringement proceeding. Second, there is NO claim element which describes the standard from which the variation is to be made. Third, even if a standard is described in terms of "normal" fibrinogen content of blood, any alteration in one component or variant, alters the percentage of at least one other of the components. The claim language does not permit interpretation of the concentrations of the components of the composition, and thus, cannot be definite because the starting material is not defined.

Claim Rejections - 35 USC § 102

Claims 2-4, 6, 9, 25-34, 36, 37 remain rejected under 35 U.S.C. 102(b) as being anticipated by US 6,946,140 [A].

The claims are directed to a method comprising: administering to a patient a fibrin matrix made by the process of
a) selecting a composition consisting of multiple variants of fibrinogen (of which one is HMW fibrinogen),
b) modifying the fibrinogen to change the relative concentration of at least one variant, and
c) forming a fibrin matrix from the composition of step b).

Since applicant states the response to the restriction requirement that there is HMW in some amount in all the elected claim methods, a change in any concentration of any variant will necessarily cause a change in the relative concentration of the HMW variant. The claims are so indefinite that the concentrations of the components of the fibrin matrix cannot be determined.

The reference is relied upon as explained below.

US 6,946,140 discloses that the application of a fibrin clot to a wound enhances healing and fibroblast migration. The disclosure teaches fractionation of fibrinogen ppt. from normal plasma and produces fibrin gels from the various fractions and tests the gels for fibroblast migration activity. See Examples 1 and 2. The fibrinogen is contacted with a wound surface.

Although the types of fibrinogen in the composition of the prior art are not always expressed in the same way as in the claimed method, and because the concentrations in the claims are expressed as relative concentrations, in the absence of evidence to the contrary, the method of the references is deemed to fall within the claim limitations because a permutation in any variant concentration will cause a relative variation in the concentration of at least one other variant in the composition. Clarification of the invention and claim language may serve to advance prosecution.

Claim Rejections - 35 USC § 103

Claims 2-4, 6, 9-12, 14-34, 36, 37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,946,140 [A] in combination with Holm *et al.* [X] or Hasegawa *et al.* [U2], Smith *et al.* [V2] or Falls *et al.* [W2] or WO 00/62833 [N].

The claims are directed to a method comprising: administering to a patient a fibrin matrix made by the process of
a) selecting a composition consisting of multiple variants of fibrinogen (of which one is HMW fibrinogen),
b) modifying the fibrinogen to change the relative concentration of at least one variant, and
c) forming a fibrin matrix from the composition of step b).

To the extent that the claimed method may be interpreted, the following references are applied.

US 6,946,140 discloses that the application of a fibrin clot to a wound enhances healing and fibroblast migration. The disclosure teaches fractionation of fibrinogen ppt. from normal plasma and produces fibrin gels from the various fractions and tests the gels for fibroblast migration activity. See Examples 1 and 2. The fibrinogen is contacted with a wound surface. A high migration rate of fibroblasts is preferred. Col. 8, l. 53 states that sample 1 of fibrinogen lacks the extended gamma chains which constitute approximately 15% of the fibrinogen in normal plasma. Sample 2 had both extended and non-extended gamma chains. Sample 4 had degraded alpha chains. All are tested for fibroblast migration.

WO 00/62833 discloses in Example 1, page 29, normal plasma which contains a mixture of fibrinogen types, precipitation by glycine, precipitation by ammonium sulfate 25% saturation which produces a purified fibrinogen with a mixture of types as evidence by fibrinogen bands I and II.

Also fractions (Sample 2) were produced from a mixture of fibrinogen types which had "all its alpha chains intact, but lacked molecules with gamma chains that have an extended carboxy terminal which constitutes approximately 15% of the fibrinogen in plasma. Another fraction was produced which had all alpha chains intact and contained molecules with both extended and non-extended gamma chains.

Also, Sample 4 contain 20-30% of molecules with degraded alpha chains. Other fractions were also produced with changes in the relative concentration of fibrinogen variants. Sample 4 was clottable.

Holm *et al.* discloses a method comprising :
selecting "normal" fibrinogen, fractionating to form fractions with more or less HMW, LMW and LMW' than the "normal" distribution (Fig 2), forming a fibrin matrix (clot) (page 171).

Hasegawa *et al.* disclose fractionating fibrinogen into fractions F1 and F2 with molecular weights of 340 and 325kDa (page 184), forming a fibrin clot (Fig. 2).

Smith *et al.* disclose producing mixtures of fibrinogen variants from purified variants (page 22081) and forming fibrin clots (Fig. 2).

Falls *et al.* disclose purifying fibrinogen to form fractions with different ratios of fibrinogen variants (p. 14252), forming fibrin clots.

The substitution of the fibrin matrices of WO 00/62833 or Holm et al. or Hasegawa et al. or Smith et al. or Falls et al. for the fibrin matrices of US 6,946,140 in a method of treating patients with wounds would have been obvious because US '140 teaches the formation of fibrin matrices with different mixtures of fibrinogen variants and their application for enhancing wound healing. In the absence of evidence to the contrary, one of ordinary skill in the art may substitute any fibrinogen fraction in a fibrin clot for application to a wound. It is noted that the specification does not contain any exemplification of wound treatment in a subject.

To the extent that the claims can be interpreted, the references are applied as explained above. Further, claims 2 and 6 merely recite desired results and as such are also rejected over the references of record.

One of ordinary skill in the art would have been motivated at the time of invention to produce this composition in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art

as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Response to Arguments

Applicant's arguments filed 7/25/08 have been fully considered but they are not persuasive.

Applicants argue that in a three component system, a rise in the level of one component does not necessarily cause any change in one of the other components. Only the concentration of two components of the three component must change. This is accepted. However, the way the claims are written, the examiner has for the sake of prosecution been reading them as being directed to "normal" concentrations of variants in blood, when the composition consisting of multiple variants of fibrinogen is selected. Thus, an addition of one variant changes the % of both the others calculated as % of total fibrinogen. Clarification and delineation and specifics might promote advancement in prosecution.

Applicants argue that US '140 does not reveal or even hint to the effects of fibrinogen composition on angiogenesis. Please note that increased angiogenesis is merely the desired effect of the method of administering a fibrin clot (matrix) with an altered fibrinogen variant composition compared to a "normal" concentration. Thus, the method of administering the same product (with an altered variant content as compared to a "normal" variant content), would be reasonably expected to yield in the same result whether or not that result is overtly recognized.

" To invalidate a patent by anticipation, a prior art reference normally needs to disclose each and every limitation of the claim. See Standard Havens Prods., Inc. v. Gencor Indus., Inc., 953 F.2d 1360, 1369, 21 USPQ2d 1321, 1328 (Fed. Cir. 1991). However, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. See id.; Verdegaal Bros., Inc. v. Union Oil Co. of Cal.,

814 F.2d 628, 630, 2 USPQ2d 1051,1053 (Fed. Cir. 1987). Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. See In re King, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. See Titanium Metals, 778 F.2d at 780. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See id. at 782. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See id. at 782 ("Congress has not seen fit to permit the patenting of an old [composition], known to others . . . , by one who has discovered its . . . useful properties."); Verdegaal Bros., 814 F.2d at 633.

This court's decision in Titanium Metals illustrates these principles. See Titanium Metals, 778 F.2d at 775. In Titanium Metals, the patent applicants sought a patent for a titanium alloy containing various ranges of nickel, molybdenum, iron, and titanium. The claims also required that the alloy be "characterized by good corrosion resistance in hot brine environments." Titanium Metals, 778 F.2d at 776. A prior art reference disclosed a titanium alloy falling within the claimed ranges, but did not disclose any corrosion-resistant properties. This court affirmed a decision of the PTO Board of Appeals finding the claimed invention unpatentable as anticipated. This court concluded that the claimed alloy was not novel, noting that "it is immaterial, on the issue of their novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties." Id. at 782. This same reasoning holds true when it is not a property, but an ingredient, which is inherently contained in the prior art. The public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." See Atlas Powder Co. v. IRECO Inc. 51 USPQ2d 1943 (Fed. Cir. 1999).

Thus, a reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

While discovery of the biological mechanism behind the administration of a known bioactive compound is clearly publishable in a peer-review journal, the criteria for patenting claims are distinct from publication criteria. For example, if the active step of the method is the same and the subject is the same, then the claimed method can be anticipated or made obvious by the prior art, even if the prior art does not recognize or appreciate this mechanism as long as the compound administered, dosage, mode of administration, subject, etc. are the same as in the method disclosed in the prior art.

If this were not so, one patent might issue with a one step claim of administering the a compound to a subject in order to empirically treat a specific disease which is result of a contemporaneously unknown, disordered mechanism or pathway; and, then upon later discovery of the mechanism of the disorder, another patent could issue with a one step claim directed to the administration of the same compound to the same subject in order to modulate the specifically disordered mechanism or pathway. This would lead to multiple patents with essentially the same invention being patented, merely being couched in different words.

The method of US '140 discloses various fibrinogen fractions and that fibrin matrix application to wounds enhances healing. In the absence of evidence concerning the differences between the cited prior art compositions and the lack of clarity of the composition of the claims, these are assumed to be the same compositions or obvious permutations of the compositions as presently administered in the claims.

Conclusion

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651
October 18, 2008